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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,957	06/18/2001	Rose Ramon Botella Mesa	229752001300	3466

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EXAMINER	
MARVICH, MARIA	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/763,957	BOTELLA MESA ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/6/06*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7,9,11-15 and 19-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 7, 9, 11-15 and 19-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are no new grounds of rejection herein and therefore, this action is final.

Claim Objections

Claim 11 is objected to because of the following informalities: claim 11 recites "comprising the promoter of claim 1, 7, 9 and 22" which should recites -- comprising the promoter of claims 1, 7, 9 and 22-- should be used.

Claim 19 is objected to because of the following informalities: claim 19 recites "a nucleic acid" however when referring to a limitation previously recited, a definite article, e.g. --the--, or the term --said-- should be used. Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 7, 9, 11-15 and 19-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid sequence defining a promoter comprising SEQ ID NO:3, does not reasonably provide enablement for said sequence with at least 90% similarity to SEQ ID NO:3 or to residues 2016-2384 of SEQ ID NO:3 or a complement of these sequences or a sequence of nucleotides that hybridize to these sequences under stringency conditions of 2X SSC, 0.1% w/v SDS and 45°C. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. **This rejection is maintained for reasons of record in the office action mailed 6/6/06 and restated below.**

1) Nature of invention. The invention is drawn to an isolated sequence that defines a promoter in which the promoter is said to direct expression of a gene encoding ACC synthase and is inducible in response to physical stimulation.

2) Scope of the invention. Applicants claim a genus of sequences that are nucleotide sequences that "define a promoter", said sequence with at least 90% similarity to SEQ ID NO:3 or to residues 2016-2384 of SEQ ID NO:3 or a complement of these sequences or a sequence of nucleotides that hybridize to these sequences under stringency conditions of 2X SSC, 0.1% w/v SDS and 45°C. Therefore, applicants recite a broad and diverse genus of sequences that are nucleotide sequences that "define a promoter", said sequence with at least 90% similarity to SEQ ID NO:3 or residues 2016-2384 of SEQ ID NO:3 or a complement of these sequences or a sequence of nucleotides that hybridize to these sequences under stringency conditions of 2X SSC, 0.1% w/v SDS and 45°C.

3) Number of working examples and guidance. Functionally, applicants disclose that sequences that "define a promoter" "confers, activates or enhances expression of a structural gene or other nucleic acid in a plant cell" (see page 16, paragraph 5). Structurally, applicants disclose the sequence of pGEL-1 (SEQ ID NO:3). pGEL-1 comprises the promoter from mung bean ACC synthase that directs expression of a protein encoded by a sequence with 100% identity to SEQ ID NO: 1. Primer pairs 4 and 5 are used to isolate the promoter from mung

bean. To characterize the promoter, applicants generate a series of seven serial deletions of the mung bean ACC synthase promoter region (page 36). A general decline in activity in the shorter promoters is detected in immature and mature leaf tissue but not evidently in any other tissues (page 37).

4) State of the art. The art does not disclose SEQ ID NO:3. Nor does the art or the specification teach the acc synthase promoter from mung bean or domains/ motifs required for promoter activity by the acc synthase promoter. Therefore, as neither domains nor structural motifs are available, the ability to identify

5) Unpredictability of the art. By reciting sequences with 90% homology to SEQ ID NO:3 or the fragment comprising residues 2016-2384 of SEQ ID NO:3, applicants recite a broad genus of promoters that can differ in any of 10% of the nucleotides of SEQ ID NO:3. Furthermore, by claiming sequences hybridizing under medium stringency conditions (according to page 13, 6X SSC, 0.1% w/v SDS and 45°C), the relationship between the structure of the sequence and its function becomes unclear. Furthermore, applicants do not provide the structural requirements of the sequences of SEQ ID NO:3 that "confers, activates or enhances expression of a structural gene or other nucleic acid in a plant cell". Therefore, it would require undue experimentation to identify those molecules that are 90% identical to SEQ ID NO:3 or that are isolated upon hybridization to SEQ ID NO:3 or homologs of SEQ ID NO:3. A person of ordinary skill in the art could not predict the operability of the species that would be isolated of sequences with at least 90% similarity or a complement of this sequence of a sequence of nucleotides that hybridize to SEQ ID NO:3 under stringency conditions of 2X SSC, 0.1% w/v

SDS at 45°C. By disclosing pGEL-1, the applicants have not reduced to practice the claimed invention.

6) Amount of Experimentation Required. The specification provides a single reference sequences without identifying relevant characteristics or structural-functional relationships. Thus neither the specification nor the prior art teach the structural requirements of sequences with at least 90% similarity to SEQ ID NO:3 or residues 2016-2384 of SEQ ID NO:3 or a complement of these sequences or a sequence of nucleotides that hybridize to these sequences under stringency conditions of 2X SSC, 0.1% w/v SDS and 45°C that encodes a promoter. Given the large size and diversity of the recited sequences, the absence of disclosed or art recognized correlations between structure and function and the large number of potential sequences or homologs, it must be considered that any sequence with promoter activity in a plant cell must be empirically determined.

Response to Amendment-35 USC 112, first paragraph

Applicants traverse the claim rejections under 35 U.S.C 35 USC 112, first paragraph on page 6-7 of the amendment filed 12/6/06. Applicants argue that promoter sequences are very flexible and can tolerate point mutations as they do not normally alter the expression intensity of pattern of expression of the promoter. Applicant's arguments filed 12/6/06 have been fully considered but they are not persuasive. The rejection is based upon consideration of the number of sequences that would be encompassed by a promoter with 90% sequence identity and the highly unpredictability nature of identifying those that are promoters. To put the situation in perspective, the number of possible nucleotide sequences of 100 nucleotides in length is 20^{100}.

The number of possible nucleotide sequences that are of a given % identity relative to a reference sequence, where all differences between the possible sequences and the reference sequence are substitutions, can be calculated by the following formula:

$$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + ... + X^{n-1}L(L-1)(L-2)...(L-(n-2))/(n-1)! + X^nL(L-1)(L-2)...(L-(n-1))/n!$$

where N is the number of possible sequences, X is the number of different nucleotides that can be substituted for a residue in the reference sequence, L is the length of the reference sequence, n is the maximum number of residues that can be inserted, deleted or substituted relative to the reference sequence at a given % identity. For an amino acid sequence, X is 19 (alternate amino acids).

For a 100 nucleotide sequence that is at least 90% identical to a reference sequence of 100 nucleotide sequence, the number of possible sequences having 9 nucleotide sequence substitutions relative to the reference (the penultimate term of the formula) is approximately 4.1 x 10^{14}. Whereas the number of possible sequences having 10 nucleotide sequence substitutions relative to the reference (the final term of the formula) is approximately 1.4 x 10^{18}. So the last term is approximately equal to N, i.e. the preceding terms contribute little to the total, and the last term of the above equation can be rewritten as $X^nL!/(L-n-1)!n!$, which is approximately equal to N.

In the present case, the reference nucleotide sequence of SEQ ID NO: 3 is 2474 nucleotides long (L), the number of possible nucleotide substitutions (X) per residue is 3, and the maximum number of substituted nucleotides (n) is 247 for 90% identity to SEQ ID NO: 3. Using the approximation formula, the number of possible nucleotide sequences that differ by up to 247

nucleotides from the 2474 reference sequence is approximately 7 x 10^{461} different nucleotide sequences having up to 274 substitutions. While limiting the scope of potential sequences to those that are at least 90% identical to a reference greatly reduces the number of potential sequences to test, it does not do so in any meaningful way. The number of nucleotide sequences that are at least 90% identical to the reference sequence greatly exceed the estimated number of atoms in the universe (10^{70} to 10^{90}). Thus, limiting the claims by the recited structural relationships merely reduces the degree of impossibility of making and testing sequences for those, which are a promoter. It would be physically impossible to make and test more than an insignificant fraction of the possible mutant proteins that are related to SEQ ID NO:3 by 90%.

Now considering isolation of promoter sequences following hybridization under stringency conditions of 2X SSC, 0.1% w/v SDS and 45°C. First, hybridization detects those sequences that have stretches of DNA in common. The result of this reaction need not comprise a promoter or promoter related sequences. For example, a sequence lacking sequences essential for promoter function can result in a nucleic acid sequence is almost 100% related sequentially to regions of SEQ ID NO: 3 but has no relationship functionally. Secondly, isolation of a promoter from such sequences requires a detailed understanding of the structural requirements of the promoter. The specification fails to convey the relevant identifying characteristics of the recited nucleic acids nor provide a description of the promoter such that the structural requirements of the promoter are known.

Conclusion

Claims 1, 7, 9, 11-15 and 19-24 are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1633

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER